IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lars E. French et al. Art Unit : 1647
Serial No. : 09/419,262 Examiner : L. Spector
Filed : October 12, 1999
Title : METHODS AND COMPOSITIONS FOR TREATING DISEASES ASSOCIATED WITH INCREASED FAS-LIGAND TITERS

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REPLY TO FINAL OFFICE ACTION DATED APRIL 11, 2003

In reply to the Final Office Action dated April 11, 2003, applicants submit the following remarks.

35 U.S.C. § 103(a)

On pages 2-3 of the Office Action, the Examiner finally rejected claims 7-20 as allegedly unpatentable over Hattori et al. (1998) Blood 91:4051 ("Hattori") in view of Lynch et al., U.S. Patent No. 5,830,469 ("Lynch"). According to the Examiner,

> Applicants argue that Lynch fails to suggest that anti-Fas antibodies can be used to treat GVHD, and teaches away from using anti-Fas antibodies in such a method. This argument has been fully considered but is not deemed persuasive because Lynch is not the primary reference in this rejection but rather the secondary reference, and is cited as teaching that treatment with anti-Fas antibodies is functionally equivalent to treatment with anti-Fas Ligand antibodies, see col. 14, lines 13-24. The fact that Lynch may treat a totally different treatment for GVHD, that of administering TNFα, which treatment functions by a distinct mechanism from that of Hattori et al, has no bearing on the instant grounds of rejection, that it would have been obvious to modify the method of Hattori et al. by substituting anti-Fas antibodies for anti-Fas ligand antibodies in view of the

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teachings of Lynch et al. Accordingly, the invention remains *prima facie* obvious over the teachings of Hattori et al. in view of Lynch et al.

Applicants respectfully traverse the rejection in view of the following comments.

Claim 13, the independent claim rejected herein, is directed to a method of treating a subject having graft-versus-host-disease (GVHD) by administering to the subject a composition containing anti-Fas antibodies in an amount effective to inhibit binding of Fas ligands to Fas receptors in the subject. In addition, dependent claims 7-12 and 14-20 require the administration of an intravenous immunoglobulin (IVIG) mixture to the subject to treat the disease.

Hattori describes the effects of the administration of neutralizing anti-Fas ligand (FasL) and/or anti-TNFα monoclonal antibodies in a mouse model of GVHD. Hattori demonstrates that either an anti-FasL or an anti-TNFα monoclonal antibody alone delays mortality and improves body weight in the mouse model, whereas co-administration of both antibodies results in a complete protection from GVHD (see, e.g., Figs. 1A and 1B of Hattori). Hattori does not suggest treating GVHD by the administration of anti-Fas antibodies.

The Examiner asserted that, in view of Lynch, it would have been obvious to modify the methods of Hattori by substituting anti-Fas antibodies for anti-FasL antibodies in the treatment of GVHD. In the response to the previous Office Action, applicants argued that Lynch teaches away from using anti-Fas antibodies for the treatment of GVHD. The Examiner has stated two grounds for not finding applicants' argument persuasive: (i) Lynch is a secondary reference in the rejection (not a primary reference); and (ii) Lynch is cited as teaching that treatment with anti-Fas antibodies is functionally equivalent to treatment with anti-FasL antibodies. These comments are addressed in the order they were raised by the Examiner.

First, it is irrelevant whether Lynch is cited as a primary or secondary reference in considering whether it teaches away from the claimed invention. Irrespective of whether a given reference is labeled as "primary" or "secondary," the Examiner must consider it in its entirety, including those portions that would lead the skilled artisan away from the claimed invention. (See MPEP § 2141.02).

Second, the Examiner has not addressed those portions of Lynch that applicants have asserted teach away from the claimed invention. As detailed in the previous response, in the

only passages in Lynch that propose a treatment for GVHD, Lynch teaches away from using anti-Fas antibodies that inhibit the binding of FasL to Fas. According to Lynch, GVHD is an example of a disease in which it is desirable to induce apoptosis of T cells (column 15, lines 21-29). Accordingly, Lynch describes treating GVHD by administering TNFα, thereby promoting apoptosis of T lymphocytes that play a role in causing the disease. Lynch nowhere suggests treating GVHD by inhibiting apoptosis and/or by administering anti-Fas antibodies to a subject. Lynch's method of treating GVHD is therefore in direct contrast to that of the claimed invention, which entails administering to a subject anti-Fas antibodies that prevent the binding of Fas-ligands to Fas receptors, thereby inhibiting apoptosis.

The Examiner is required to consider Lynch as a whole, including those portions of the reference teaching away from the claimed invention. (MPEP § 2141.02). There is no suggestion to combine if a reference teaches away from its combination with another source. (Tec Air, Inc. v. Denso Manufacturing Inc., 192 F.3d 1353, 1360 (Fed. Cir. 1999)). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by applicant." (Id., citing In re Gurley 27. F.3d 551, 553 (Fed. Cir. 1994)). As detailed herein, Lynch leads the skilled artisan to treat GVHD by promoting apoptosis of T lymphocytes, rather than by inhibiting apoptosis according to the claimed methods. The mechanism of treating GVHD disclosed by Lynch is clearly divergent from the mechanism used by applicants and embodied in the pending claims. Accordingly, the combination of Hattori and Lynch would not have supplied the skilled artisan, at the time of the filing of the present application, with the requisite suggestion to use anti-Fas antibodies in a method of treating GVHD. Applicants request that the Examiner withdraw the rejection.

In addition to the above, dependent claims 7-12 and 14-20 require the administration of an IVIG mixture to the subject to treat GVHD. Nothing in Hattori and/or Lynch suggests that IVIG, a blood product obtained from plasma of healthy donors, can be administered to a subject to treat GVHD. Accordingly, claims 7-12 and 14-20 are patentable over the cited references for this separate reason, independent of the comments provided above with respect to claim 13 from which they depend. Applicants request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Enclosed is a Petition for One Month Extension of Time. Please charge the One Month Extension of Time fee of $55 (as well as any other charges or credits) to Deposit Account No. 06-1050, referencing Attorney Docket No. 11141-003001.

Respectfully submitted,

Date: August 11, 2003

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